UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,447	02/07/2008	Steffen Goletz	107753-001 BSL	5668

27387 7590 04/09/2012

LONDA, BRUCE S.
NORRIS MCLAUGHLIN & MARCUS, PA
875 THIRD AVE, 8TH FLOOR
NEW YORK, NY 10022

EXAMINER	
CHANDRA, GYAN	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
04/09/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,447	GOLETZ ET AL.	
	Examiner	Art Unit	
	GYAN CHANDRA	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *9,12-18 and 24-37* is/are pending in the application.

5a) Of the above claim(s) *12-18 and 36* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *9,24-30,32,33,35 and 37* is/are rejected.

8)☒ Claim(s) *31 and 34* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 1/26/2012 is acknowledged and fully considered.

Status of Application, Amendments, And/Or Claims

The addition of claim 37 is made of record.

Claims 9, 12-18 and 24-37 are pending.

Claims 12-18 and 36 remain withdrawn for the reasons of record on page 2 of the office action of 8/26/2011.

Claims 9, 24-35 and 37 are under examination.

Response to Arguments

Claim Rejections *- maintained*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9, 24-30, 33 remain rejected and newly added claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Betenbaugh (WO 00/52135, see IDS) for the reasons of record on pg. 3-6 of the office action of 8/26/2011 and as discussed below.

The instant claims are broadly drawn to a process for the production of a highly active glycoprotein comprising:
expression of a highly active glycoprotein in an expression cell line, harboring at least one defect in the sugar nucleotide biosynthetic pathway of sialic acids and which is transfected with nucleic acid encoding the glycoprotein, in a medium supplemented with a concentration of at least one sialic acid precursor additive, the concentration being determined by a process comprising: (i) expression of a plurality of different sialylation forms of said glycoprotein by differential sialylation using different concentrations of at least one sialic acid precursor; and (ii) determination of the activity of the different sialylation forms in comparison with a reference glycoprotein in (a) suitable bioassay(s); and (iii) selection of the sialylation form with the higher/highest activity and determination of the concentration of the sialic acid precursor additive(s) which is correlated with the higher/highest activity level of said glycoprotein, wherein a partially sialylated glycoprotein is produced, wherein a sialic acid precursor additive is used which results in glycoproteins with natural sialic acid modifications

Applicants argue (see Response of 1/26/2012) that the claimed process employs which controls the degree of sialylation in contrast to Benebaugh's process. They argue that Betenbaugh uses genetically engineered insect cells to attach sialic acids to

glycoproteins and that is obtained by adding key precursor such as ManNAc. Applicants argue that Betenbaugh et al does not disclose how the activity of a glycoprotein may be optimized by comparing the formed sialylated glycoprotein to a reference protein and selecting the glycoprotein with a higher activity. They argue that the present invention uses human cells that are selected to have a defect in sialylation activity via addition of the sialic acid precursor. They argue that Betenbaugh is teaching away from the present invention as they use an insect cell line which is using glycosylated protein to less glycosylated protein. They argue that the present invention is drawn to use NM-F9 cells generated from wild-type NM cells for their ability not to sialyte a protein. They argue that the reference Bonig is directed to glycosylation and not to control the degree of sialylation. Applicants argue that CHO cells may not produce the same sialylation of a protein as produced in NM-F9 cells.

Applicants' arguments have been fully considered but they are not persuasive because Betenbaugh teaches expressing a human transferrin protein in insect cell T. ni cell which has defect in adding sialic acid to a glycoprotein (page 73). Betenbaugh teaches that in insect cells, N-linked glycans attached to heterologous or homologous glycoproteins comprise either high mannose (Man9-5GlcNAc2) or truncated (Nan3-2GlcNAc2) oligosaccharides; occasionally comprising alpha(1,6)-fucose. Betenbaugh teaches that T. ni cell (insect cell) show presence of limited level of partially elongated hybrid structures with one terminal Man branch and one branch with term Gal, GalNAc or another sugar and complex N-linked oligosaccharide (page 3, lines 16+). Betenbaugh teaches that production of sialylation of a recombinant protein (plasminogen) is

observed in baculovirus-infected insect cells. Betenbaugh say that insect cells generate very little sialic acid compared to mammalian CHO cells (page 5, lines 17+). It is possible that similar lack or limitation may be observed in eukaryotes as well (page 5, lines 20+). Therefore, Betenbaugh suggests co-expressing sialyltransferase and other transferases and the proper acceptor substrates in order for production of sialylated and other complex glycoproteins in eukaryotes (page 5, lines23+). Betenbaugh teaches that manipulating carbohydrate processing pathways in inset and other eukaryotic cells so that the cells produce complex sialylated glycoproteins is useful for enhancing the value of eukaryotic expression system and increasing the application of heterologous cell expression products as vaccines, therapeutics, and diagnostic tools; and for lowering the biotechnology costs, since particular expression system can be selected based on efficiency of production rather than the capacity to produce particular glycoforms (page 6, lines15+). Betenbaugh teaches cell culture and quantitation of sialic acid (see page 87). Betenbaugh teaches doing in vitro activity from infected cells (page 87). Betenbaugh teaches that cell lines can be assessed for N-glycans attached to glycoproteins using techniques disclosed on page 57. Betenbaugh teaches to use a cell of interest which expresses the enzymeGlcNAc-2 epimerase (see claim 5 and 10). Betenbaugh teaches to use ManNAc supplementation to obtain substantial level of New5Ac levels (page 78, lines23+). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., use NM-F9 cells generated from wild-type NM cells for their ability not to sialylate a protein) are not recited in the rejected claim(s), for

examples see claim 9. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, the claims do not recite any specific sialylation pattern of GM-CSF which may not be produced on CHO cells or insect cells taught by Betenbaugh.

Claim 32 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Betenbaugh (WO 00/52135, see IDS) in view of Muramatsu et al (J. Biochem. 94:799-810, 1983) and Foglin et al (Electronic J. of Biotech. 5: 243-250, 2002) for the reasons of record on page 7-8, however the rejection of claims 31 and 34 is withdrawn in view of Applicants' statement of Muramatsu that F9 cells are murine embryonal cells having ATCC accession number CRL-1720.

Applicants argue that Betenbaugh et al do not teach sialylation of GM-CSF using NM-F9 cells.

Applicants' arguments have been fully considered but they are not persuasive because the features upon which applicant relies (i.e., use NM-F9 cells generated from wild-type NM cells for their ability not to sialyte a protein) are not recited in the rejected claim(s), for examples see claim 9. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claim 35 remain rejected under 35 U.S.C. 102(b) as being anticipated by Fogolin et al (Electronic J. of Biotech. 5: 243-250, 2002).

The instant claim is drawn to glycoprotein GM-CSF which is producible by the process of claim 34.

Applicants argue that the proteins differ substantially in their carbohydrate structures and since GM-CSF produced by Foglin is produced in a non-human CHO or COS cells, the GM-CSF produced in NM-CSF would be different.

Applicants' arguments have been fully considered but they are not persuasive because the claim as recited does not have any structural feature of GM-CSF produced by the process of claim 34 which differs from the GM-CSF taught by Foglin, unless evidence to contrary.

Claim 35 remain rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter for the reasons of record on page.9 of the office action of 8/26/11.

Applicants argue that glycoproteins differ in their glycosylation pattern depending on which cell line is used for the production and they argue that HEK293 cell is used for the production of GM-CSF from Sigma which is different from the instant cell line NM-F9 and therefore, the product may be different.

Applicants' arguments have been fully considered but they are not persuasive because claim 35 as recited does not have any structural feature of GM-CSF produced by the process of claim 34 which differs from the GM-CSF sold by Sigma Aldrich Catalog.

Conclusion

Claims 9, 24-30, 32, 33, 35 and 37 are rejected.

Claims 31 and 34 are objected for depending from a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GYAN CHANDRA whose telephone number is (571)272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vanessa Ford can be reached on (571) 272-0857. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gyan Chandra/
Primary Examiner, Art Unit 1646